

Quantitative structure–fungicidal activity relationships of *N*-(4-difluoromethoxybenzyl)-pyrimidin-4-amines against wheat and barley fungi

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Abstract: A set of *N*-(4-difluoromethoxybenzyl)pyrimidinamines with various substituents at the 4- and 5-positions of the pyrimidine ring and at the benzyl position were prepared, and their fungicidal activities against wheat brown rust, *Puccinia recondita*, and barley powdery mildew, *Erysiphe graminis*, were measured. Variations in each of these activities were quantitatively analysed by the use of physicochemical substituent parameters and a regression analysis. Each of these activities was parabolically correlated with the steric bulkiness of the pyrimidine substituents and with the bulkiness or the hydrophobicity of the benzylic substituents.

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1 INTRODUCTION

A number of fungicides with specific modes of action have been developed. Sterol 14 α -demethylation inhibitors (DMIs) are the largest group of modern fungicides.¹ Resistance to fungicides, including DMIs, is a crucial problem, and much effort has been expended to prepare new types of compound. Successful examples are amine-type fenpropimorph and fenpropidin, which inhibit sterol biosynthesis but are not DMIs.^{2,3} A new class of carbocation-mimetic ergosterol biosynthesis inhibitors has also been prepared.⁴ These are used as substitutes for DMIs.

We have found *N*-benzyl-4-pyrimidinamines to have a broad spectrum of pesticidal activity.⁵ We extended the research to prepare *N*-polyfluorophenoxy or *N*-difluoromethoxybenzyl-4,5-disubstituted pyrimidinamines and found that the latter are a promising series of compounds to control wheat brown rust and barley powdery mildew.⁶ We recently prepared a number of difluoromethoxybenzylamino-pyrimidines and developed one of them, diflumetorim, for practical use.⁷ We have analysed the fungicidal activities of this series of compounds by using physicochemical substituent parameters and a regression analysis, and report here that there is an optimum steric dimension in the combined set of substituents on the pyrimidine moiety and an optimum steric and/or

hydrophobicity of the substituent at the benzyl position.

2 MATERIALS AND METHODS

2.1 Synthesis of compounds

Compounds **4**, **5**, and **10** were the same samples as those previously reported.⁶ The other compounds listed in Table 1 were prepared by the reaction shown in Fig 1. Compounds **I** shown in Fig 1 were prepared by previously described methods.⁶ Compounds **II** were taken from reagent stocks in our laboratory. The chemical structures of the newly prepared compounds were confirmed by 270 MHz-[¹H]NMR spectroscopy (GX270, JEOL, Tokyo, Japan) in deuteriochloroform, using tetramethylsilane as the internal standard, or by mass spectroscopy (M-80, Hitachi, Tokyo). Melting points were measured with a melting point apparatus (Buchi 535, Flawil, Switzerland). Refractive indexes were measured with a refractometer (3T, Atago-Abbe, Tokyo). The melting points and refractive indexes of the compounds are listed in Table 1. Elemental analyses were in accordance with the proposed structures. Typical examples for compounds **20** and **24** are as follows. Other compounds were prepared according to one of these two procedures.

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<i>N</i> _o	Substituent			<i>log K</i>	<i>log P</i>	<i>mp</i> (°C) or <i>n</i> _D (at°C)
	<i>R</i> ₁	<i>R</i> ₂	<i>R</i> ₃			
1	CH ₃	F	CH ₃	0.042	—	1.5407(26)
2	CH ₃	F	C ₂ H ₅	—	—	1.5298(30)
3	CH ₃	Cl	H	0.100	3.24 ^b	71–72
4	CH ₃	Cl	CH ₃	0.263	3.76	1.5521(29)
5	CH ₃	Cl	C ₂ H ₅	0.417	4.17	1.5471(24)
6	CH ₃	Cl	<i>o</i> -C ₃ H ₇	0.433	4.27	1.5576(23)
7	CH ₃	Cl	<i>i</i> -C ₃ H ₇	0.530	4.56 ^c	1.5378(26)
8	C ₂ H ₅	F	CH ₃	0.188	—	1.5251(24)
9	C ₂ H ₅	Cl	H	0.269	—	70–72
10	C ₂ H ₅	Cl	CH ₃	0.430	4.26	1.5442(30)
11	C ₂ H ₅	Cl	C ₂ H ₅	0.579	—	1.5487(23)
12	C ₂ H ₅	Cl	<i>o</i> -C ₃ H ₇	0.597	—	1.5582(24)
13	C ₂ H ₅	Br	CH ₃	0.517	—	1.5358(28)
14	C ₂ H ₅	C ₂ H ₅	CH ₃	0.113	—	77–79
15	CH ₂ Cl	Cl	C ₂ H ₅	0.439	—	1.5649(21)
16	CH ₂ OCOCH ₃	Cl	C ₂ H ₅	0.289	3.75	1.5441(21)
17	CH(OCH ₃) ₂	Cl	C ₂ H ₅	0.270	—	1.5355(26)
18	C ₂ F ₅	Cl	CH ₃	0.795	—	1.4942(23)
19	Cl	Cl	CH ₃	0.398	—	1.5566(24)
20	Cl	C ₃ H ₇	C ₂ H ₅	0.588	4.96	55–58
21	Cl	C ₄ H ₉	C ₂ H ₅	0.767	—	1.5380(27)
22	C ₃ H ₇	Cl	CH ₃	0.590	4.73	1.5418(24)
23	—S—CH=CH—		CH ₃	0.088	—	145
24	—S—CH=CH—		C ₂ H ₅	0.215	4.40	1.6058(28)
25	—S—CH=C(CH ₃)—		C ₂ H ₅	0.436	—	1.5912(25)
26	—(CH ₂) ₃ —		CH ₃	−0.021	3.70	125–129
27	—(CH=CH) ₂ —		C ₂ H ₅	0.172	4.26	114–116
28	—CH=CFCH=CH—		C ₂ H ₅	0.334	4.76	127–130

Table 1. Physical properties of *N*-(4-difluoromethoxybenzyl)pyrimidin-4-amines^a

^a General structure is shown in Fig 1.

^b From eqn (3).

^c From eqn (4).

2.1.1 6-Chloro-*N*-(α -[*RS*]ethyl-4-difluoromethoxybenzyl)-5-propylpyrimidin-4-amine (20)

A solution of α -[*RS*]ethyl-4-difluoromethoxybenzylamine (1.6 g; 7.9 mmol) and 4,6-dichloro-5-propylpyrimidine (1.5 g; 7.9 mmol) in triethylamine (15 ml) was stirred at room temperature. After 8 h, the triethylamine was removed under reduced pressure. The residue was purified by column chromatography (Wako Gel C200, Wako, Osaka, Japan) using toluene+ethyl acetate (20+1 by volume) as an eluent to give 0.39 g (15% yield) of light yellowish crystals. *Mp* 55–58°C, [¹H]NMR (δ ppm, CDCl₃): 0.99 (3H, t, *J*=7.2 Hz), 1.64 (2H, q, *J*=7.2 Hz), 1.92 (2H, m), 2.62 (3H, m), 4.99 (1H, d, *J*=7.2 Hz), 5.18 (1H, q, *J*=7.6 Hz), 6.49 (1H, t, *J*=7.4 Hz), 7.11 (2H, d, *J*=8.8 Hz), 7.32 (2H, d, *J*=8.8 Hz), 8.21 (1H, s).

2.1.2 *N*-(α -[*RS*]ethyl-4-difluoromethoxybenzyl)-thieno[2,3-*d*]pyrimidin-4-amine (24)

To a solution of α -[*RS*]ethyl-4-difluoromethoxybenzylamine (3.5 g; 17.6 mmol), triethylamine (5 ml) and 4-chlorothieno[2,3-*d*]pyrimidine (3.0 g; 17.6 mmol) in toluene (30 ml), a catalytic amount of *N,N*-dimethylpyridin-4-amine was added. The mixture was refluxed for 5 h. After cooling, the reaction mixture was washed with water, and the organic layer was dried over anhydrous sodium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by column chromatography (Wako Gel C200) using toluene+ethyl acetate (4+1 by volume) as an eluent to give 2.7 g (46% yield) of a colorless oily

product. *n*_D²⁸ 1.6058. [¹H]NMR (δ ppm, CDCl₃): 0.98 (3H, t, *J*=7.2 Hz), 2.01 (2H, m), 5.33 (1H, q, *J*=7.2 Hz), 5.44 (1H, d, *J*=7.2 Hz), 6.49 (1H, t, *J*=7.4 Hz), 7.09 (2H, d, *J*=8.8 Hz), 7.18 (1H, d, *J*=8.0 Hz), 7.28 (1H, d, *J*=8.0 Hz), 7.39 (2H, d, *J*=8.8 Hz), 8.47 (1H, s).

2.2 Fungicidal tests

The procedures were essentially the same as those reported.⁶

2.2.1 Wheat brown rust

In a plastic planting pot (6 cm diameter \times 10 cm), 10 wheat seedlings (*Triticum aestivum* L) were grown at 28°C. At the 1.5-leaf stage on average, an aqueous dispersion of a wettable powder of the test compounds was sprayed over the plants. Two days later, the wheat plants were inoculated by a spore suspension of wheat brown rust, *Puccinia recondita* Rob ex Desm, at 7×10^4 spores ml^{−1}. One week later, the symptoms of the first leaf were examined. The activity rankings of the test

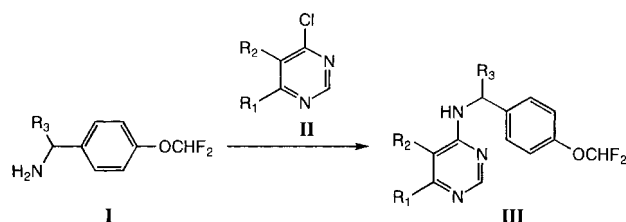


Figure 1. Synthetic route for test compounds.

Table 2. Fungicidal activities and substituent parameters of *N*-(4-difluoromethoxybenzyl)pyrimidin-4-amines^a

No	Substituents			<i>pI</i> ₄ (M)				Parameters			
				WBR ^b		BPM ^c					
	<i>R</i> ₁	<i>R</i> ₂	<i>R</i> ₃	<i>Obsd</i>	<i>Calcd</i> ^d	<i>Obsd</i>	<i>Calcd</i> ^e	ΔVw_1	ΔVw_2	Δk_1	Δk_2
1	CH ₃	F	CH ₃	3.08	3.58	3.17	3.65	1.45	1.02	0.00	1.63
2	CH ₃	F	C ₂ H ₅	3.43	3.42	4.02	3.85	1.45	2.05	0.00	3.17
3	CH ₃	Cl	H	3.05	2.90	3.00	2.86	2.07	0.00	2.21	0.00
4	CH ₃	Cl	CH ₃	4.20	4.30	4.20	4.19	2.07	1.02	2.21	1.63
5	CH ₃	Cl	C ₂ H ₅	4.22	4.14	4.54	4.38	2.07	2.05	2.21	3.17
6	CH ₃	Cl	<i>o</i> -C ₃ H ₇	4.23	4.06	4.55	4.20	2.07	2.38	2.21	3.30
7	CH ₃	Cl	<i>i</i> -C ₃ H ₇	3.20	3.23	3.32	3.44	2.07	3.07	2.21	4.30
8	C ₂ H ₅	F	CH ₃	4.19	4.55	4.19	4.37	2.47	1.02	1.46	1.63
9	C ₂ H ₅	Cl	H	3.07	3.23	3.05	3.07	3.09	0.00	3.85	0.00
10	C ₂ H ₅	Cl	CH ₃	4.82	4.63	4.82	4.40	3.09	1.02	3.85	1.63
11	C ₂ H ₅	Cl	C ₂ H ₅	4.83	4.47	4.55	4.60	3.09	2.05	3.85	3.17
12	C ₂ H ₅	Cl	<i>o</i> -C ₃ H ₇	4.85	4.39	4.05	4.41	3.09	2.38	3.85	3.30
13	C ₂ H ₅	Br	CH ₃	4.87	4.53	4.59	4.30	3.40	1.02	4.75	1.63
14	C ₂ H ₅	C ₂ H ₅	CH ₃	4.51	3.72	3.91	3.59	4.28	1.02	0.71	1.63
15	CH ₂ Cl	Cl	C ₂ H ₅	3.96	4.49	2.86	4.62	2.88	2.05	2.43	3.17
16	CH ₂ OCOCH ₃	Cl	C ₂ H ₅	4.29	3.02	<2.89	3.32	4.63	2.05	0.93	3.17
17	CH(OCH ₃) ₂	Cl	C ₂ H ₅	2.89	2.62	<2.89	2.98	4.85	2.05	0.74	3.17
18	C ₂ F ₅	Cl	CH ₃	3.10	3.60	<2.82	3.49	4.36	1.02	7.53	1.63
19	Cl	Cl	CH ₃	4.29	4.14	3.80	4.08	1.90	1.02	3.56	1.63
20	Cl	C ₃ H ₇	C ₂ H ₅	3.41	3.77	4.05	3.97	4.11	2.05	3.92	3.17
21	Cl	C ₄ H ₉	C ₂ H ₅	<2.87	2.04	<2.87	2.50	5.13	2.05	5.71	3.17
22	C ₃ H ₇	Cl	CH ₃	3.50	3.93	3.32	3.77	4.11	1.02	5.48	1.63
23	—S—CH=CH—		CH ₃	4.34	3.98	4.21	3.61	2.19	1.02	0.46	1.63
24	—S—CH=CH—		C ₂ H ₅	4.23	3.82	4.23	3.80	2.19	2.05	0.19	3.17
25	—S—CH=C(CH ₃)—		C ₂ H ₅	3.64	4.00	<2.85	3.88	3.30	2.05	2.40	3.17
26	—(CH ₂) ₃ —		CH ₃	4.28	4.18	3.15	3.75	2.57	1.02	−0.63	1.63
27	—(CH=CH) ₂ —		C ₂ H ₅	3.92	4.06	3.64	3.96	2.72	2.05	−0.24	3.17
28	—CH=CFCH=CH—		C ₂ H ₅	3.69	4.07	3.84	3.95	3.05	2.05	1.38	3.17

^a General structure is shown in Fig 1.^b Wheat brown rust (*Puccinia recondita*).^c Barley powdery mildew (*Erysiphe graminis* f sp *hordei*).^d From eqn (8).^e From eqn (10).

chemicals were defined on a scale of zero to five, corresponding to 0–30, 31–60, 61–80, 81–94, 95–99 and 100% prevention, respectively. The test was done with two pots for each concentration of each compound.

2.2.2 Barley powdery mildew

The preventive activity against the barley powdery mildew, *Erysiphe graminis* DC f sp *hordei* Marchal, was similarly determined by using 10 barley seedlings (*Hordeum vulgare* L var *vulgare*) per pot and conidial spores of the fungus. The activity rankings of the test chemicals were defined in the same way as for the activity against wheat brown rust.

2.3 Correlation analysis

2.3.1 Structure–activity relationships

Variations in the fungicidal activity, *pI*₄, which will be defined below, were analysed with physicochemical parameters of substituents *R*₁–*R*₃ and a regression analysis by eqn (1).^{8,9}

$$pI_4 = a\Delta Vw - b(\Delta Vw)^2 + c\Delta k - d(\Delta k)^2 + \text{constant} \quad (1)$$

ΔVw is the summation of the van der Waals volume of

*R*₁ and *R*₂ (ΔVw_1) or the volume of substituents *R*₃ (ΔVw_2) relative to that of H scaled by 0.1 to make it nearly equiscalar with *pI*₄ values. The *Vw* values were calculated according to the reported method.¹⁰ The ΔVw values are listed in Table 2. Δk is the hydrophobic substituent parameter defined below. The squared ΔVw and Δk terms were added to identify their optimum values, so that *b* and *d* ≥ 0. The *a*, *b*, *c*, *d*, and constant in eqn (1) were calculated by regression analysis. The level of significance of each term in the equations was examined by the *t*-test. Unless otherwise noted, all of the correlation equations and all of the terms in each equation were justified above the 95% level.

2.3.2 Hydrophobicity parameter

Δk in eqn (1) is the hydrophobic substituent parameter for the sum of *R*₁ and *R*₂ (Δk_1) and for *R*₃ (Δk_2). The retention factor (*k'*) in high-performance liquid chromatography (HPLC) is defined by eqn (2):

$$k' = (t_R - t_0)/t_0 \quad (2)$$

where *t*_R is the retention time of the test compound and *t*₀ is that of a non-retained reference, potassium iodide. The log *k'* values are listed in Table 1. HPLC was carried

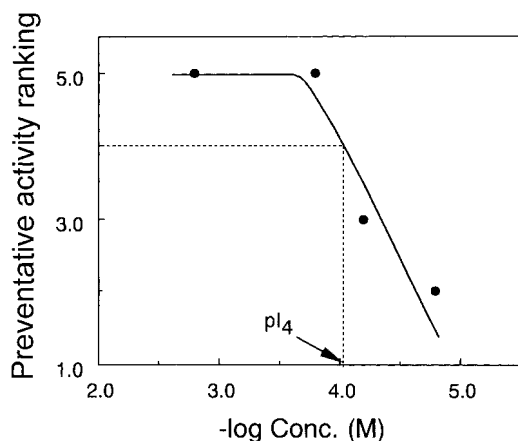


Figure 2. Preventative activity ranking, I_4 , of compound 2 against barley powdery mildew.

out with an LC-10AS liquid chromatograph and a CTO-10A column oven (Shimadzu, Kyoto, Japan) connected with an SPD-10A UP-VIS detector (Shimadzu) operated at 245 nm. The column (250 × 4.8 mm ID) was packed with a Column Capcell Pack C18 (Shiseido, Tokyo). For the HPLC analysis, a mixture of a methanol solution of test compounds and an aqueous solution of potassium iodide (7 + 3 by volume) was injected on the column and eluted with methanol + water (7 + 3 by volume) at a flow rate of 1 ml min⁻¹ at 40 °C. Δk_1 was calculated based on the difference of $\log k'$ for each compound from a compound where R_1 is CH₃, R_2 is F, and R_3 is comparable to both. The difference was multiplied by 10 to make Δk_1 equiscalar with pI_4 values. Similarly, Δk_2 was calculated from the $\log k'$ values for each compound and a compound with R_3 = H as the reference. The Δk_1 and Δk_2 values are listed in Table 2.

For some compounds, the $\log P$ value was experimentally determined by the shake-flask method in a 1-octanol/water partitioning system. $\log k'$ for compound 7 was estimated to be 0.530 from a linear $\log k'$ - $\log P$ relationship for the homologous compounds 3–6 (s = 0.010, r = 0.999). For the estimation, the $\log P$ values of compounds 3 and 7 were calculated by eqns (3) and (4), respectively:

$$\log P(\text{compound 3}) = \log P(\text{compound 4}) - \pi\text{CH}_3 \quad (3)$$

$$\begin{array}{ccc} 3.24 & 3.76 & 0.52 \end{array}$$

$$\log P(\text{compound 7}) = \log P(\text{compound 5}) - \pi\text{CH}_3 - F_{\text{cBr}} \quad (4)$$

$$\begin{array}{ccc} 4.56 & 4.17 & 0.52 \quad 0.13 \end{array}$$

where F_{cBr} is a correction factor for the branching of substituents in the additivity principle of the hydrophobicity.¹¹ The $\log P$ and estimated $\log k'$ values are listed in Table 1.

3 RESULTS

3.1 Fungicidal activities

The preventative action of the compounds against

both fungi was mostly concentration-dependent. From the concentration-preventative ranking relationship as exemplified in Fig 2 for compound 2 against barley powdery mildew, the concentration to give the activity ranking 4 (95–99% prevention) was defined as I_4 (M). The pI_4 values for test compounds against both fungi, which are reciprocal log values of I_4 , are given in Table 2.

The pI_4 values of each compound were not much different between the fungi. Compounds 15, 16, and 26 were exceptions in which the preventative activity against wheat brown rust was 10 times or more than that against barley powdery mildew.

When R_1 and R_2 were kept constant, the activity values were changed with substituent R_3 , giving a maximum activity value with a moderate size of substituents (compounds 5 and 6 among compounds 3–7; compounds 10 and 11 among compounds 9–12). The introduction of substituents R_1 (compounds 16 and 17) and R_2 (compound 21) with a large size seemed to be unfavorable to increase in activity. The introduction of some fused ring systems to the pyrimidine ring was moderately favorable to increase the activity against both fungi (compounds 23, 24, and 28), but the introduction of other fused ring systems was favorable only against wheat brown rust (compounds 25–27).

3.2 Quantitative analysis of substituent effects on fungicidal activities

3.2.1 Wheat brown rust

Compounds without a fused ring system in the pyrimidine moiety were selected first for the analysis. Variations in the potency of compounds for which the fungicidal activity values against wheat brown rust ($pI_4(\text{WBR})$) were determinable were quantitatively analyzed using eqn (1) to give eqn (5) as the best equation.

$$\begin{aligned} pI_4(\text{WBR}) = & -1.012(\pm 2.337) + 2.795(\pm 1.491)\Delta V_{\text{w1}} \\ & -0.460(\pm 0.238)(\Delta V_{\text{w1}})^2 \\ & +1.268(\pm 0.708)\Delta k_2 - 0.268(\pm 0.164)(\Delta k_2)^2 \\ n = 21, s = 0.471, r = 0.791, F(4, 16) = 6.67 \quad (5) \end{aligned}$$

In eqn (5) and the following equations, n is the number of compounds, s is the standard deviation, r is the correlation coefficient, and F is the value of the ratio between the regression and residual variances. The figures in parentheses following each coefficient are the 95% confidence intervals of the regression coefficients. A close inspection of the results showed that the experimentally measured $pI_4(\text{WBR})$ value for compound 16 was markedly higher than that calculated by eqn (5). This deviation might be due to a specific feature of the R_1 substituent, which may be easily hydrolysed during the course of interaction with the receptor, giving a biologically weak compound. By

Table 3. Squared correlation (r^2) matrix for variables used to derive eqn (8)

	ΔVw_1	$(\Delta Vw_1)^2$	ΔVw_2	$(\Delta Vw_2)^2$	Δk_1	$(\Delta k_1)^2$	Δk_2	$(\Delta k_2)^2$
$(\Delta Vw_1)^2$	0.976							
ΔVw_2	0.001	0.001						
$(\Delta Vw_2)^2$	0.007	0.007	0.914					
Δk_1	0.212	0.179	0.030	0.021				
$(\Delta k_1)^2$	0.247	0.233	0.049	0.054	0.839			
Δk_2	0.000	0.000	0.989	0.862	0.036	0.052		
$(\Delta k_2)^2$	0.003	0.003	0.947	0.973	0.033	0.065	0.924	
I_F	0.011	0.025	0.019	0.005	0.242	0.121	0.029	0.016

excluding this compound, eqn (5) was improved to give eqn (6).

$$\begin{aligned} \text{pI}_4(\text{WBR}) = & -1.437(\pm 2.051) + 3.169(\pm 1.326)\Delta Vw_1 \\ & -0.535(\pm 0.214)(\Delta Vw_1)^2 \\ & + 1.322(\pm 0.614)\Delta k_2 - 0.288(\pm 0.143)(\Delta k_2)^2 \\ n = 20, s = 0.405, r = 0.858, F(4, 15) = 10.44 \quad (6) \end{aligned}$$

Equation (6) means that variations in the fungicidal potency against wheat brown rust were parabolically related to the volume of R_1 and R_2 in terms of ΔVw_1 with a $(\Delta Vw_1)_{\text{opt}}$ value of 3.0, and to the hydrophobicity of R_3 in terms of Δk_2 with a $(\Delta k_2)_{\text{opt}}$ value of 2.3.

The addition of six fused-type compounds **23–28** regarding the pyrimidine moiety to eqn (6) gave eqn (7).

$$\begin{aligned} \text{pI}_4(\text{WBR}) = & -0.372(\pm 1.923) + 2.483(\pm 1.239)\Delta Vw_1 \\ & -0.426(\pm 0.200)(\Delta Vw_1)^2 \\ & + 1.211(\pm 0.605)\Delta k_2 - 0.276(\pm 0.140)(\Delta k_2)^2 \\ n = 26, s = 0.425, r = 0.785, F(4, 21) = 8.45 \quad (7) \end{aligned}$$

A close inspection of the results showed that the activity values of these fused compounds were mostly lower than those calculated by eqn (7). By using an indicator variable, an improved eqn (8) was derived.

$$\begin{aligned} \text{pI}_4(\text{WBR}) = & -0.975(\pm 1.911) + 2.902(\pm 1.242)\Delta Vw_1 \\ & -0.498(\pm 0.202)(\Delta Vw_1)^2 \\ & + 1.352(\pm 0.587)\Delta k_2 - 0.303(\pm 0.134)(\Delta k_2)^2 \\ & -0.412(\pm 0.430)I_F \\ n = 26, s = 0.397, r = 0.825, F(5, 20) = 8.52 \quad (8) \end{aligned}$$

In this and the following equations, I_F takes unity for the fused compounds **23–28** but is zero for other compounds. The substitution of the steric parameter term(s) by hydrophobicity parameter term(s) for the corresponding substituents and/or the reverse substitution did not improve eqn (8). Equation (8) means that variations in the fungicidal activity were parabolically related to the volume of R_1 and R_2 with a $(\Delta Vw_1)_{\text{opt}}$ value of 2.9, and to the hydrophobicity of R_3 with a $(\Delta k_2)_{\text{opt}}$ value of 2.2. Even though the I_F

term in eqn (8) was justified at the 94% level of significance, the term means that the compounds with the fused ring system on the pyrimidine ring were two or three times less active than others when other structural factors were the same. Table 3 shows the intercorrelation of variables used to derive eqn (8). The $\text{pI}_4(\text{WBR})$ values calculated by eqn (8) are listed in Table 2.

3.2.2 Barley powdery mildew

Variations in the fungicidal activity of nonfused-type compounds having a definitive activity value against barley powdery mildew ($\text{pI}_4(\text{BPM})$) were quantitatively analysed. No significant correlation equation was yielded by including all of these compounds, however. A close inspection of the results showed that the activity value of compound **15** was markedly lower than that calculated from the tentatively obtained insignificant correlation equations (data not shown). By excluding compound **15**, eqn (9) was yielded as the best.

$$\begin{aligned} \text{pI}_4(\text{BPM}) = & -0.637(\pm 2.043) + 2.613(\pm 1.432)\Delta Vw_1 \\ & -0.454(\pm 0.249)(\Delta Vw_1)^2 \\ & + 1.884(\pm 0.705)\Delta Vw_2 - 0.551(\pm 0.231)(\Delta Vw_2)^2 \\ n = 17, s = 0.319, r = 0.882, F(4, 12) = 10.55 \quad (9) \end{aligned}$$

By including the fused-type compounds with a definitive activity value by the use of an indicator variable I_F , eqn (10) was yielded as the most significant equation, although the number of compounds is slightly smaller than one would like.

$$\begin{aligned} \text{pI}_4(\text{BPM}) = & -0.150(\pm 2.306) + 2.290(\pm 1.625)\Delta Vw_1 \\ & -0.404(\pm 0.284)(\Delta Vw_1)^2 \\ & + 1.861(\pm 0.811)\Delta Vw_2 - 0.545(\pm 0.266)(\Delta Vw_2)^2 \\ & -0.652(\pm 0.472)I_F \\ n = 22, s = 0.378, r = 0.802, F(5, 16) = 5.76 \quad (10) \end{aligned}$$

Without the indicator variable term, no significant equation was yielded. The substitution of the steric parameter term(s) by hydrophobicity parameter term(s) for the corresponding substituents did not improve eqn (10). Equation (10) means that variations in the fungicidal activity against barley powdery

Table 4. Squared correlation (r^2) matrix for variables used to derive eqn (10)

	ΔVw_1	$(\Delta Vw_1)^2$	ΔVw_2	$(\Delta Vw_2)^2$	Δk_1	$(\Delta k_1)^2$	Δk_2	$(\Delta k_2)^2$
$(\Delta Vw_1)^2$	0.978							
ΔVw_2	0.008	0.009						
$(\Delta Vw_2)^2$	0.018	0.020	0.910					
Δk_1	0.256	0.232	0.012	0.004				
$(\Delta k_1)^2$	0.337	0.321	0.024	0.021	0.886			
Δk_2	0.006	0.006	0.989	0.856	0.018	0.028		
$(\Delta k_2)^2$	0.014	0.016	0.943	0.975	0.009	0.028	0.917	
I_F	0.007	0.018	0.014	0.002	0.358	0.222	0.023	0.010

mildew were parabolically related to the summed volume of R_1 and R_2 with a $(\Delta Vw_1)_{\text{opt}}$ value of 2.8, and to the hydrophobicity of R_3 with a $(\Delta k_2)_{\text{opt}}$ value of 1.7. The I_F term means that the introduction of a fused-ring system to the pyrimidine moiety decreases the activity by a factor of five. Table 4 shows the intercorrelation of variables used to derive eqn (10). The $pI_4(\text{BPM})$ values calculated by eqn (10) are listed in Table 2.

4 DISCUSSION

The hydrophobicity parameter values, Δk , were basically calculated from $\log k'$. The experimentally measured pK_a values for compounds **5**, **20**, and **27** were 4.5, 2.6, and 6.0, respectively; thus, we suspected that all of the test compounds used in this study are mostly in the neutral form under the conditions of both the HPLC analysis and bioassays. For compounds for which both $\log P$ and $\log k'$ values were available, an excellent eqn (11) was yielded.

$\log P =$

$$2.892(\pm 0.132) + 3.206(\pm 0.299) \log k' + 0.827(\pm 0.117) I_F$$

$$n = 13, s = 0.071, r = 0.991, F(2, 10) = 288.0 \quad (11)$$

Without the I_F term, the quality of the correlation was much poorer ($s = 0.342$, $r = 0.747$) than that in eqn (11). Equation (11) shows that the $\log P$ value of the present set of compounds can be well predicted from the $\log k$ value when the presence of the fused-ring system in the pyrimidine moiety is considered separately.

Among the nonfused-type compounds **1–22**, R_1 was

mostly CH_3 or C_2H_5 and R_2 was mostly halogens. The number of compounds was too small to allow the use of independent parameters for substituents R_1 and R_2 . Therefore, we attempted to use parameters evaluated for the combined set of R_1 and R_2 to reduce the number of parameters. As a result, steric parameters in terms of ΔVw were useful to derive eqns (8) and (10) for fungicidal activities against wheat brown rust and barley powdery mildew, respectively. Because of the definition, we could not differentiate the position specificity of R_1 and R_2 . Additionally, we used only alkyl derivatives at R_3 . Although we successfully showed the optimum steric bulkiness and the hydrophobicity for R_3 in eqns (8) and (10), respectively, these results seemed not to be conclusive because of the high collinearity between ΔVw_2 and Δk_2 (Tables 3 and 4). To solve these problems, one should extend the analysis by increasing the number of compounds so as to be able to use independent parameters for R_1 and R_2 and to lower the collinearity between parameters for R_3 .

As a counterpart of eqn (10) that was derived for the fungicidal activity against barley powdery mildew, we obtained eqn (12) without the use of the indicator variable term.

$pI_4(\text{BPM}) =$

$$2.324(\pm 0.608) + 0.529(\pm 0.296) \Delta k_1 - 0.095(\pm 0.062) (\Delta k_1)^2 + 1.861(\pm 0.740) \Delta Vw_2 - 0.565(\pm 0.247) (\Delta Vw_2)^2$$

$$n = 22, s = 0.352, r = 0.819, F(4, 17) = 8.63 \quad (12)$$

Although it is statistically more significant than eqn (10), eqn (12) did not give reasonable $pI_4(\text{BPM})$ values for most of the weakly active compounds (Table 5). Therefore, we concluded that eqn (10) is the most reasonable equation for this activity.

In summary, we conducted the quantitative analyses of the fungicidal activities of the *N*-benzylpyrimidinamines against wheat and barley fungi. The activity values of diflumetorim (compound **5**), which was recently developed for practical use by our group, were well predicted by the correlation equations.

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Table 5. Comparison of the fungicidal activity of very active compounds against barley powdery mildew and those calculated from eqns (10) and (12)

No	pI_4 (M)		
	Obsd	Calcd ^a	Calcd ^b
16	<2.89	3.32	4.17
17	<2.89	2.98	4.10
18	<2.82	3.49	2.24
21	<2.87	2.50	3.69
25	<2.85	3.88	4.49

^a From eqn (10).

^b From eqn (12).

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